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| EXAMINER |
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| ART UNIT | PAPER NUMBER |
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| 1642 | |

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16

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application N . | Applicant(s) | |
|---|---|---|---|
| | 09/894,657 | HILLMAN ET AL. | |
| | Examiner | Art Unit | |
| | Alana M. Harris, Ph.D. | 1642 | |

*-- The MAILING DATE of this c mmunication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *14 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,10,29-44,51 and 52* is/are pending in the application.

4a) Of the above claim(s) *1,29,32,34,43,44 and 51* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10, 30, 31, 33, 35-42 and 52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

### *Election/Restrictions*

1. Applicant's election with traverse of Group VI (claims 10, 30, 31, 33, 35-42 and 52) in Paper No. 15 is acknowledged. The traversal is on the ground(s) that:

(1) the prior art searches for the claims of Groups I-II and IV-VI would substantially overlap; and

(2) the subject matter of Groups I-III were already searched in an ancestor application. Applicants also recite the election of species requirement and requirements for Markush group practice. This is not found persuasive because the Examiner did not set forth an election of species, but an election/restrictions requirement. While Applicants' claims did recite a few sequences (three) they were not so closely related that a search and examination of the entire claim would be made without serious burden. The sequence homology alignment between Applicants' SEQ ID NO: 1, 3 and 5 does not reveal high sequence similarity, hence the sequences were deemed separate and patentably distinct, see attached database sheet labeled "seq1-3_5.res". MPEP 803.2 cites that "A Markush-type claim can include independent and distinct inventions. This is true where two or more of the members are so unrelated and diverse that a prior art reference anticipating the claim with respect to one of the members would not render the claim obvious under 35 U.S.C. 103 with respect to the other member(s)."

Moreover, as to the question of burden of search, the claims of the remaining Groups, are classified and subclassified differently, necessitating different searches in

the U.S. Patent shoes. Further, classification of subject matter is merely one indication of the burdensome nature of the search involved. The literature search, particularly relevant in this art, is not co-extensive and is much more important in evaluating the burden of search. Clearly different searches and issues are involved in the examination of each group. For these reasons the restriction requirement set forth in Paper number 9, mailed December 2, 2002 is deemed to be proper and is adhered to.

The requirement is still deemed proper and is therefore made FINAL. Further, Groups VII-XII involve various method steps, which require additional searching.

However, the policies set forth in the Commissioner's Notice of February 28, 1996 published on March 26, 1996 at 1184 O.G. 86 will be followed. Method claims limited to the scope of the allowable product claims will be rejoined and examined at the time the product claims are indicated as being allowable.

2. Claims 1, 10, 29-44, 51 and 52 are pending.

Claims 1, 29, 32, 34, 43, 44 and 51, drawn to non-elected inventions are withdrawn from examination.

Claims 2-9, 11-28 and 45-50 have been cancelled.

Claims 10, 30, 31, 33, 35-42 and 52 are examined on the merits.

Claim 51 will not examined with Group VI because the said Group reads on SEQ ID NO: 5 and not SEQ ID NO: 3 as set forth in claim 51.

***Information Disclosure Statement***

3. The information disclosure statement (IDS) filed June 28, 2001 makes note that copies of the cited references where not included with the instant application because they were previously cited by or submitted to the Office in parent application serial number 08/985,335, filed December 4, 1997. The parent application was not available at the time of examination. The Examiner will review the entire IDS once it becomes available.

***Claim Rejections - 35 USC § 101***

4. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

5. Claims 10, 30, 31, 33, 35-42 and 52 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a substantial asserted utility or a well established utility.

The limitations of claim 1 are read into the examined claims. Claim 1 is broadly drawn to a naturally-occurring amino acid sequence having at least 90% sequence identity to the sequence of SEQ. ID. NO: 5 and a biologically active fragment and an immunogenic fragment of polypeptide, SEQ ID NO: 5. Claims 10, 30, 31, 33, 35-42 and 52 are directed to an antibody that binds SEQ ID NO:5 and methods of making the said antibody. The specification discloses the isolation of a nucleic acid, SEQ ID NO: 4, which encodes a protein, SEQ ID NO:5, see pages 3 and 4. SEQ ID NO: 5 is also known as APOP-3 (see bridging paragraph of pages 2 and 3). The protein is disclosed to have significant chemical and structural homology with a mouse apoptosis-associated protein, MA-3, see page 17, lines 18-21 and Figure 8A and 8B. Based on these similarities, the specification asserts that the newly disclosed protein has the utility of having similar activities of MA-3 influencing cell proliferation and apoptosis, see page 2, lines 14-26.

The assertion that the disclosed protein has biological activities similar to known MA-3 is not credible in the absence of supporting evidence, because the relevant literature reports numerous examples of polypeptide families wherein individual members have distinct, and even opposite, biological activities. For example, Tischer et al. (U.S. Patent 5,194,596) establishes that VEGF (a member of the PDGF, or platelet-derived growth factor, family) is mitogenic for vascular endothelial cells but not for vascular smooth muscle cells, which is opposite to the mitogenic activity of naturally occurring PDGF which is mitogenic for vascular smooth muscle cells but not for vascular endothelial cells (column 2, line 46 to column 3, line 2). The differences

between PDGF and VEGF are also seen *in vivo*, wherein endothelial-pericyte associations in the eye are disrupted by intraocular administration of PDGF but accelerated by intraocular administration of VEGF (Benjamin et al., 1998, Development 125:1591-1598; see Abstract and pp. 1594-1596). Vukicevic et al. (1996, PNAS USA 93:9021-9026) disclose that OP-1, a member of the TGF-β family of proteins, has the ability to induce metanephrogenesis, whereas closely related TGF-β family members BMP-2 and TGF-β1 had no effect on metanephrogenesis under identical conditions (p. 9023, paragraph bridging columns 1-2). See also Massague, who reviews other members of the TGF-β family (1987, Cell 49:437-8, esp. p. 438, column 1, second full paragraph to the end). Similarly, PTH and PTHrP are two structurally closely related proteins, which can have opposite effects on bone resorption (Pilbeam et al., 1993, Bone 14:717-720; see p. 717, second paragraph of Introduction). Finally, Kopchick et al. (U.S. Patent 5,350,836) disclose several antagonists of vertebrate growth hormone that differ from naturally occurring growth hormone by a single amino acid (column 2, lines 37-48).

Generally, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. For example, Skolnick et al. (2000, Trends in Biotech. 18:34-39) state that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function (see Box 2, p. 36). Similarly, Bork (2000, Genome Research 10:398-400) states that the error rate of functional annotations in the sequence database is considerable, making it even more

difficult to infer correct function from a structural comparison of a new sequence with a sequence database (see especially p. 399). Such concerns are also echoed by Doerks et al. (1998, Trends in Genetics 14:248-250) who state that (1) functional information is only partially annotated in the database, ignoring multi functionality, resulting in underpredictions of functionality of a new protein and (2) overpredictions of functionality occur because structural similarity often does not necessarily coincide with functional similarity. Smith et al. (1997, Nature Biotechnology 15:1222-1223) remark that there are numerous cases in which proteins having very different functions share structural similarity due to evolution from a common ancestral gene. Brenner (1999, Trends in Genetics 15:132-133) argues that accurate inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene superfamilies in nature, and then most homologs must have different molecular and cellular functions. Bork et al. (1996, Trends in Genetics 12:425-427) add that the software robots that assign functions to new proteins often assign a function to a whole new protein based on structural similarity of a small domain of the new protein to a small domain of a known protein. Such questionable interpretations are written into the sequence database and are then considered facts. Finally, Bowie et al. (1990, Science 247:1306-1310) state that determination of three dimensional structures from primary sequence database (see especially p. 399). Such concerns are also echoed by Doerks et al. (1998, Trends in Genetics 14:248-250) who state that (1) functional information is only partially annotated in the database, ignoring multi functionality, resulting in underpredictions of functionality of a new protein and (2) overpredictions of functionality

occur because structural similarity often does not necessarily coincide with functional similarity. Smith et al. (1997, Nature Biotechnology 15:1222-1223) remark that there are numerous cases in which proteins having very different functions share structural similarity due to evolution from a common ancestral gene. Brenner (1999, Trends in Genetics 15:132-133) argues that accurate inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene superfamilies in nature, then most homologs must have different molecular and cellular functions. Bork et al. (1996, Trends in Genetics 12:425-427) add that the software robots that assign functions to new proteins often assign a function to a whole new protein based on structural similarity of a small domain of the new protein to a small domain of a known protein. Such questionable interpretations are written into the sequence database and are then considered facts. Finally, Bowie et al. (1990, Science 247:1306-1310) state that determination of three dimensional structures from primary amino acid sequence, and the subsequent inference of detailed aspects of function from structure is extremely complex and unlikely to be solved in the near future (p. 1306). Thus, the specification fails to support the asserted credible, specific and substantial utility of the polypeptide as having the activity similar to MA-3.

The specification does not support a credible, specific and substantial utility regarding the claimed antibodies because the polypeptide to which the antibody binds does not have a substantial and credible utility. The specification asserts that "Northern analysis shows the expression of APOP-3 in various cDNA libraries, at least 48% of which are immortalized or cancerous, and at least 30% of which involve immune

response, and at least 8% of which are expressed in fetal/infant tissues or organs.", see page 17, lines 21-24. This assay seem to be unrelated to the proposed utility of using APOP-3 molecules for diagnosis of conditions or disorders which are associated with the expression of APOP, see bridging paragraph of pages 42 and 43. However, the specification does not disclose a correlation between any specific disorder and an altered level or form of SEQ ID NO: 5. Also, the specification does not predict whether the polypeptide would be overexpressed or underexpressed in a specific, diseased tissue compared to the healthy tissue control.

The instant application has failed to provide guidance as to how one of skill in the art could use the claimed invention in a way that constitutes a credible, specific and substantial utility. The proposed uses of the claimed invention are simply starting points for further research and investigation into potential practical uses of the claimed polypeptides. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner v. Manson*, 148 USPQ at 696.

### *Claim Rejections - 35 USC § 112*

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 10, 30, 31, 33, 35-42 and 52 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific

asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

8. Claims 10, 30, 31, 33, 35-42 and 52 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The limitations of claim 1 are read into the examined claims. Claim 1 is broadly drawn to "a naturally-occurring amino acid sequence having at least 90% sequence identity to the sequence of SEQ. ID. NO: 5" and biologically-active and immunogenic fragments. Claims 10, 30, 31, 33, 35-42 and 52 are drawn to antibodies (i.e. monoclonal, humanized and polyclonal) and methods of making the said antibodies that specifically bind the fragments listed in claim 1. Claim 10 is broadly drawn to an isolated antibody that specifically binds to a purified polypeptide comprising an amino acid sequence selected from a naturally-occurring amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO: 5, biologically-active fragment of the amino acid sequence of SEQ ID NO: 5 and an immunogenic fragment of the amino acid sequence of SEQ ID NO: 5. These claims are drawn to antibodies that are to bind SEQ ID NO: 5 and polypeptide fragments that possibly contain a small number of amino acid residues that is less than the 469 amino acids. Hence the claims are drawn to antibodies that bind amino acid residues that minimally contain only portions of SEQ ID

NO: 5. Thus, the claims are drawn to a large genus of molecules. In the case of antibodies that allegedly bind small identified amino acid residues claimed with open language, the genus of polypeptides comprising only a partial sequence encompasses a variety of subgenera with widely varying attributes. The specification discloses only the alleged structural features of one species of antibody, those that bind the polypeptide sequences of SEQ ID NO: 5. The specification lacks information to lead one of skill in the art to understand that the applicant had possession of the broadly claimed invention at the time the instant application was filed. Applicant is referred to the interim guidelines concerning compliance with the written description requirement of 35 U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 10, 30, 31, 33, 35-42 and 52 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claim 10 is vague and indefinite because it depends from non-elected claim 1. For examination purposes, the limitations of non-elected claim 1 will be read into the examined claims. Applicants may obviate this rejection by rewriting the claim in independent form.

***Claim Rejections - 35 USC § 102***

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

12. Claims 10, 35, 36 and 52 are rejected under 35 U.S.C. 102(a) as being anticipated by Matsuhashi et al. (Research Communications in Biochemistry and Cell & Molecular Biology 1(1): 109-120, 1997). Matsuhashi discloses a biologically active fragment, an immunogenic fragment, as well as a naturally occurring polypeptide comprising an amino acid sequence 96% identical to amino acid sequence, SEQ ID NO: 5, see page 113 and attached database sheet. The disclosed polypeptide is termed H731. An anti-H731 protein antibody (RA) was prepared by immunizing rabbits with the disclosed protein, page 110, Materials and Methods section. Accordingly, the disclosed polyclonal antibody is the same as the claimed invention and hence anticipatory.

***Claim Rejections - 35 USC § 103***

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. Claims 10, 35, 36 38, 39 and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Matsuhashi et al. (Research Communications in Biochemistry and Cell & Molecular Biology 1(1): 109-120, 1997), in view of Campbell (Ailsa M. (Laboratory Techniques in Biochemistry and Molecular Biology 13:1-32, 1984). Matsuhashi discloses a biologically active fragment, an immunogenic fragment, as well as a naturally occurring polypeptide comprising an amino acid sequence 96% identical to amino acid sequence, SEQ ID NO: 5, see page 113 and attached database sheet. The disclosed polypeptide is termed H731. An anti-H731 protein antibody (RA) was prepared by immunizing rabbits with the disclosed protein, page 110, Materials and Methods section. Accordingly, the disclosed polyclonal antibody is the same as the claimed invention and hence anticipatory. Matsuhashi does not teach a monoclonal antibody which specifically binds to the polypeptide comprising the amino acid sequence of SEQ ID NO: 5 or to the recited fragments of the polypeptide.

However, Campbell teaches a strategy to generate antibodies, as well as methods for producing hybridomas, procedures of monoclonal antibody production in mice and monoclonal antibodies from hybridoma cell lines with high biological activity (e.g. affinity, specificity, etc.), see page 3, Figure 1.1. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to utilize the teachings of both, the referenced patent and Campbell. In addition Campbell states on page 29, Section 1.3.4 "It is customary now for any group working on a macromolecule to both clone the genes coding for it and make monoclonal antibodies to it (sometimes without a clear objective for their application)." One of ordinary skill in the

art would have been motivated to immunize an animal, such as a rat with the polypeptide comprising the amino acid sequence of SEQ ID NO: 5 or a fragment of the polypeptide to aid in the establishment of hybridomas secreting antibodies able to bind with high specificity.

15. Claims 10, 38, 39 and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Onishi et al. (Biochem. Biophys. Res. Commun. 228:7-13, 1996/ IDS reference #8), in view of Campbell (Ailsa M. (Laboratory Techniques in Biochemistry and Molecular Biology 13:1-32, 1984). Onisha teaches a biologically-active fragment, an immunogenic fragment and a naturally occurring polypeptide comprising an amino acid sequence at least 90% identical to SEQ ID NO: 5, see page 11, Figure 5 and attached database sheet, Accession number P97296. Onishi does not teach a monoclonal antibody which specifically binds to the polypeptide comprising the amino acid sequence of SEQ ID NO: 5 or to the recited fragments of the polypeptide.

However, Campbell teaches a strategy to generate antibodies, as well as methods for producing hybridomas, procedures of monoclonal antibody production in mice and monoclonal antibodies from hybridoma cell lines with high biological activity (e.g. affinity, specificity, etc.), see page 3, Figure 1.1. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to utilize the teachings of both, the referenced patent and Campbell. In addition Campbell states on page 29, Section 1.3.4 "It is customary now for any group working on a macromolecule to both clone the genes coding for it and make monoclonal antibodies to

it (sometimes without a clear objective for their application)." One of ordinary skill in the art would have been motivated to immunize an animal, such as a rat with the polypeptide comprising the amino acid sequence of SEQ ID NO: 5 or a fragment of the polypeptide to aid in the establishment of hybridomas secreting antibodies able to bind with high specificity.

16. Claims 10, 38, 39 and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shibahara et al. (Gene 166: 297-301, 1995/ IDS reference #7), in view of Campbell, Ailsa M. (Laboratory Techniques in Biochemistry and Molecular Biology 13:1-32, 1984). Shibahara teach a biologically-active fragment, an immunogenic fragment and a naturally occurring polypeptide comprising an amino acid sequence at least 90% identical to SEQ ID NO: 5, see page 299, Figure 1 and attached database sheet, Accession number Q61823. Shibahara does not teach a monoclonal antibody which specifically binds to the polypeptide comprising the amino acid sequence of SEQ ID NO: 5 or to the recited fragments of the polypeptide.

However, Campbell teaches a strategy to generate antibodies, as well as methods for producing hybridomas, procedures of monoclonal antibody production in mice and monoclonal antibodies from hybridoma cell lines with high biological activity (e.g. affinity, specificity, etc.), see page 3, Figure 1.1. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to utilize the teachings of both, the referenced patent and Campbell. In addition Campbell states on page 29, Section 1.3.4 "It is customary now for any group working on a

macromolecule to both clone the genes coding for it and make monoclonal antibodies to it (sometimes without a clear objective for their application)." One of ordinary skill in the art would have been motivated to immunize an animal, such as a rat with the polypeptide comprising the amino acid sequence of SEQ ID NO: 5 or a fragment of the polypeptide to aid in the establishment of hybridomas secreting antibodies able to bind with high specificity.

17. Claims 10, 30, 35, 36 and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Matsuhashi et al. (Research Communications in Biochemistry and Cell & Molecular Biology 1(1): 109-120, 1997), and in view of Bird et al. (Science 242:423-242, 1988). The teachings of Matsuhashi have been presented in the 102(a) rejection. Matsuhashi does not teach a single chain antibody which specifically binds to the polypeptide comprising the amino acid sequence of SEQ ID NO:5 or to the recited fragments of the polypeptide.

However, Bird teaches the production of a single-chain antigen-binding protein and efficacy of single-chain antibodies. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to produce single-chain antibodies. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by teachings in Bird that single-chain antibodies are advantageous because of their small size, lower background in imaging applications, less immunogenic and ability to be designed with specialized function, see page 426, column 1.

18. Claims 10, 30, 38, 39 and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Onishi et al. (Biochem. Biophys. Res. Commun. 228:7-13, 1996/ IDS reference #8) or Shibahara et al. (Gene 166: 297-301, 1995/ IDS reference #7) in view of Campbell , Ailsa M. (Laboratory Techniques in Biochemistry and Molecular Biology 13:1-32, 1984) as applied to claims 10, 38, 39 and 52 above, and further in view of Bird et al. (Science 242:423-242, 1988). The teachings of Onishi, Shibahara and Campbell have been presented in the 103(a) rejections above. These references do not teach a single chain antibody which specifically binds to the polypeptide comprising the amino acid sequence of SEQ ID NO:5 or to the recited fragments of the polypeptide.

However, Bird teaches the production of a single-chain antigen-binding protein and efficacy of single-chain antibodies. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to produce single-chain antibodies. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by teachings in Bird that single-chain antibodies are advantageous because of their small size, lower background in imaging applications, less immunogenic and ability to be designed with specialized function, see page 426, column 1.

19. Claims 10, 35, 36, 41, 42 and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Matsuhashi et al. (Research Communications in Biochemistry and Cell & Molecular Biology 1(1): 109-120, 1997), in view of Huse et al. (Science 246:1275-1281, December 8, 1989). Matsuhashi teaches a biologically-active fragment, an

immunogenic fragment of SEQ ID NO: 5 and a naturally occurring polypeptide comprising an amino acid sequence at least 90% identical to SEQ ID NO: 5 and a corresponding polyclonal antibody. Matsuhashi does not teach antibodies produced by screening a Fab expression library or a recombinant immunoglobulin library, wherein the said antibodies specifically bind to the polypeptide comprising the amino acid sequence of SEQ ID NO:5 or to the recited fragments of the polypeptide.

However, Huse teaches procedures for the generation of Fab fragments and a large combinatorial library of the immunoglobulin repertoire in phage lambda. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to produce Fab fragments, catalytic and other antibodies. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by teachings in Huse that the applicability of such a screening library in the generation and construction of bacteriophage lambda libraries enables the expression of a population of functional antibody fragments with potential diversity (see page 1276, column 1, first full paragraph) and these types of antibodies are useful in diagnostics and biosensors (see page 1280, column 2, last paragraph).

20. Claims 10, 38, 39, 41, 42 and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Onishi et al. (Biochem. Biophys. Res. Commun. 228:7-13, 1996/ IDS reference #8) or Shibahara et al. (Gene 166: 297-301, 1995/ IDS reference #7) in view of Campbell , Ailsa M. (Laboratory Techniques in Biochemistry and Molecular Biology 13:1-32, 1984) as applied to claims 10, 38, 39 and 52 above, and further in view of

Huse et al. (Science 246:1275-1281, December 8, 1989). The teachings of Onishi, Shibahara and Campbell have been presented in the 103(a) rejections above. These references do not teach antibodies produced by screen a Fab expression library or a recombinant immunoglobulin library, wherein said antibodies specifically bind to the polypeptide comprising the amino acid sequence of SEQ ID NO: 5 or to the recited fragments of the polypeptide.

However, Huse teaches procedures for the generation of Fab fragments and a large combinatorial library of the immunoglobulin repertoire in phage lambda. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to produce Fab fragments, catalytic and other antibodies. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by teachings in Huse that the applicability of such a screening library in the generation and construction of bacteriophage lambda libraries enables the expression of a population of functional antibody fragments with potential diversity (see page 1276, column 1, first full paragraph) and these types of antibodies are useful in diagnostics and biosensors (see page 1280, column 2, last paragraph).

21. Claims 10, 30, 31, 33, 35, 36 and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Matsuhashi et al. (Research Communications in Biochemistry and Cell & Molecular Biology 1(1): 109-120, 1997), in view of U.S. Patent number 6,180,370 (filed June 7, 1995). Matsuhashi teaches a biologically-active fragment, an immunogenic fragment of SEQ ID NO: 5 and a naturally occurring polypeptide

comprising an amino acid sequence at least 90% identical to SEQ ID NO: 5 and a corresponding polyclonal antibody. Matsuhashi does not teach labeled, chimeric or humanized antibodies, which specifically bind to the polypeptide comprising the amino acid sequence of SEQ ID NO:5 or to the recited fragments of the polypeptide.

However, U.S. Patent #6,180,370 teaches the production of chimeric antibodies (see column 11, lines 55-67) and humanized antibodies (see column 11, line 1-column 12, lines 4). The patent also teaches several composition formulations comprising the said antibodies and acceptable excipients, as well as labels, which can be joined to the antibodies, see column 19, line 35-column 20, line 31. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to produce and design chimeric and humanized antibodies and label and produce a therapeutic admixture comprising the said antibodies. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by teachings in the patent that the applicability of such manufactured antibodies would provide antibodies specific to a predetermined antigen with strong affinity, see bridging paragraph of columns 10 and 11. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by additional teachings in the patent that antibodies taught in patent '370 could be comprised with an acceptable excipient within a composition for therapeutic and diagnostic purposes.

22. Claims 10, 30, 31, 33, 38, 39 and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Onishi et al. (Biochem. Biophys. Res. Commun. 228:7-13,

1996/ IDS reference #8) or Shibahara et al. (Gene 166: 297-301, 1995/ IDS reference #7) in view of Campbell , Ailsa M. (Laboratory Techniques in Biochemistry and Molecular Biology 13:1-32, 1984) as applied to claims 10, 38, 39 and 52 above, and further in view of U.S. Patent number 6,180,370 (filed June 7, 1995). The teachings of Onishi, Shibahara and Campbell have been presented in the 103(a) rejections above. These references do not teach labeled, chimeric or humanized antibodies, which specifically bind to the polypeptide comprising the amino acid sequence of SEQ ID NO:5 or to the recited fragments of the polypeptide.

However, U.S. Patent #6,180,370 teaches the production of chimeric antibodies (see column 11, lines 55-67) and humanized antibodies (see column 11, line 1-column 12, lines 4). The patent also teaches several composition formulations comprising the said antibodies and acceptable excipients, as well as labels, which can be joined to the antibodies, see column 19, line 35-column 20, line 31. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to produce and design chimeric and humanized antibodies and label and produce a therapeutic admixture comprising the said antibodies. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by teachings in the patent that the applicability of such manufactured antibodies would provide antibodies specific to a predetermined antigen with strong affinity, see bridging paragraph of columns 10 and 11. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by additional teachings in the patent that

antibodies taught in patent '370 could be comprised with an acceptable excipient within a composition for therapeutic and diagnostic purposes.

23. Claims 10, 31, 35-37 and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Matsuhashi et al. (Research Communications in Biochemistry and Cell & Molecular Biology 1(1): 109-120, 1997), in view of Harlow and Lane (Antibodies, A Laboratory Manual, Cold Spring Harbor Laboratory, 1988). As previously discussed the aforementioned reference a biologically-active fragment, an immunogenic fragment of SEQ ID NO: 5 and a naturally occurring polypeptide comprising an amino acid sequence at least 90% identical to SEQ ID NO: 5 and a corresponding polyclonal antibody. Matsuhashi does not teach the anticipated antibody in a composition such as an adjuvant contained with saline, mineral oil or aluminum hydroxide.

Harlow and Lane teach the said antibodies in a pharmaceutically acceptable diluent, such as Freund's adjuvant. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to formulate a pharmaceutical composition comprising a carrier/excipient and the antibodies of claims 10 and 36 in order to store the antibodies in solution for the purpose of making an adjuvant. One of ordinary skill in the art would have been motivated to store the polypeptides in saline because Harlow and Lane teach that these components are necessary when producing an effective adjuvant. Moreover, one of ordinary skill in the art would have had a reasonable expectation of success in placing the said antibodies in a pharmaceutically acceptable carrier such as saline because this protocol is a

standardly used immunological technique described in basic antibodies manual such as Harlow and Lane.

Because pharmaceutically acceptable carriers such as sterile saline solution and phosphate-buffered-saline solution were well known in the art, one of ordinary skill would have known how to formulate a pharmaceutical composition comprising a carrier/excipient and the instantly claimed antibodies.

When the claim is directed to a product, the preamble or intended use is generally nonlimiting if the body of the claim is directed to an old composition and the preamble merely recites a property inherent in the old composition. [*Kropa v. Robie*, 88 USPQ 478, 480 - 81 (CCPA 1951); see also MPEP 2111.02]. Thus, art which reads on a compound may also be applied to pharmaceutical compositions consisting essentially of said compound and a suitable pharmaceutical carrier.

It has been held by the Court that a compound and a carrier are obvious, if it is obvious in the art to utilize a carrier with related compounds. See In re Rosicky, 125 USPQ 341 (CCPA 1960).

24. Claims 10, 35-40 and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Onishi et al. (Biochem. Biophys. Res. Commun. 228:7-13, 1996/ IDS reference #8) or Shibahara et al. (Gene 166: 297-301, 1995/ IDS reference #7) in view of Campbell , Ailsa M. (Laboratory Techniques in Biochemistry and Molecular Biology 13:1-32, 1984) as applied to claims 10, 38, 39 and 52 above, and further in view of of Harlow and Lane (Antibodies, A Laboratory Manual, Cold Spring Harbor Laboratory,

1988). The teachings of Onishi, Shibahara and Campbell have been presented in the 103(a) rejections above. These references do not teach a method of preparing a polyclonal antibody which specifically binds to the polypeptide comprising the amino acid sequence of SEQ ID NO: 5 or to the recited fragments of the polypeptide, nor the said antibodies in a composition such as an adjuvant contained with saline, mineral oil or aluminum hydroxide.

Harlow and Lane teach the production of polyclonal antibodies and the said antibodies in a pharmaceutically acceptable diluent, such as Freund's adjuvant. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to produce polyclonal antibodies in order for functional and clinical studies as well as the formulation a pharmaceutical composition comprising a carrier/excipient and the said antibodies in order to store the polypeptides in solution for the purpose of making an adjuvant. One of ordinary skill in the art would have been motivated to store the polypeptides in saline because Harlow and Lane teach that these components are necessary when producing an effective adjuvant. Moreover, one of ordinary skill in the art would have had a reasonable expectation of success in placing the antibodies in a pharmaceutically acceptable carrier such as saline because this protocol is a standardly used immunological technique described in basic antibodies manual such as Harlow and Lane.

Because pharmaceutically acceptable carriers such as sterile saline solution and phosphate-buffered-saline solution were well known in the art, one of ordinary skill

would have known how to formulate a pharmaceutical composition comprising a carrier/excipient and the instantly claimed polypeptides.

When the claim is directed to a product, the preamble or intended use is generally nonlimiting if the body of the claim is directed to an old composition and the preamble merely recites a property inherent in the old composition. [*Kropa v. Robie*, 88 USPQ 478, 480 - 81 (CCPA 1951); see also MPEP 2111.02]. Thus, art which reads on a compound may also be applied to pharmaceutical compositions consisting essentially of said compound and a suitable pharmaceutical carrier.

It has been held by the Court that a compound and a carrier are obvious, if it is obvious in the art to utilize a carrier with related compounds. See In re Rosicky, 125 USPQ 341 (CCPA 1960).

25. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alana M. Harris, Ph.D. whose telephone number is (703) 306-5880. The examiner can normally be reached on 6:30 am to 4:00 pm, with alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, Ph.D. can be reached on (703) 308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4315 for regular communications and (703) 308-4315 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

ALANA HARRIS
PATENT EXAMINER

Alana M. Harris, Ph.D.
June 30, 2003